1 of 3
#31

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Jordan J.N. Tang and Arun K. Ghosh

Serial No.: 09/506,988 Art Unit: 1625

Filed: February 11, 2000 Examiner: M. Seaman

For: *"PROTEASE INHIBITORS THAT OVERCOME DRUG RESISTANCE"*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-12 in the Office Action mailed October 31, 2002, in the above-identified patent application. A Notice of Appeal was mailed on February 28, 2003. A check in the amount of $160.00 for the filing of this Appeal Brief for a small entity is also enclosed.

Please address all future correspondence to:

Patrea L. Pabst
Holland & Knight LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, GA 30309-3400

(404) 817–8473
(404) 817-8588 (fax)

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real parties in interest of this application are the assignees Oklahoma Medical Research Foundation and The Board of Trustees of the University of Illinois.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1, 2, 4-8, and 10-12 are pending and on appeal. The text of each claim on appeal is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was mailed on January 31, 2003. In the Advisory Action mailed February 19, 2003, the Examiner indicated that this amendment would not be entered. An appendix sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

The claims are directed to an aspartic protease inhibitor comprising two or more transition state isosteres (page 5, lines 23-26). The aspartic protease inhibitor may be, for example, an HIV protease inhibitor (page 10, lines 7-31) such as UIC-98-056 (Example 1 and

Example 2). The transition state isostere of the inhibitor may be, for example, -CH(OH)-CH_2- (page 4, lines 27-29) or may contain two other kinds of isosteres substituted in place of -CH(OH)-CH_2- (claim 6 as originally filed).

The claims are also directed to a method for treating patients infected with a pathogen that expresses an aspartic acid protease (page 12, lines 26-29 and claim 7 as originally filed). The method comprises the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres (page 12, lines 28-29 and page 5, lines 23-26). The inhibitor may be, for example, an HIV protease inhibitor (page 10, lines 7-31) or UIC-98-056 (Example 1 and Example 2). The transition state isostere may be, for example, -CH(OH)-CH_2- (page 4, lines 27-29) or may contain two other kinds of isosteres substituted in place of -CH(OH)-CH_2- (claim 6 as originally filed).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1, 2, 4-8, and 10-12 are enabled as required by 35 U.S.C. § 112, first paragraph;

(2) whether claims 1, 2, 4-8, and 10-12 are clear and definite as required by 35 U.S.C. § 112, second paragraph; and

(3) whether claims 1, 2, 4-8, and 10-12 were properly rejected under 35 U.S.C. § 102(b) as lacking novelty over U.S. Patent Nos. 5,491,149 and 5,683,999 to Jadhav *et al.* ("Jadhav 1" and "Jadhav 2", respectively).

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claim 1, (2) claims 2 and 6, (3) claims 4-5 (4) claim 7, and (4) 8, 10-12. Claim 1 is directed towards a protease inhibitor comprising two or more isosteres. Claims 2 and 6 are directed to the inhibitors as comprising isosteres such as $-CH(OH)-CH_2-$, or substitutions thereof. Claims 4-5 are directed to inhibitors as UIC-98-056, that may inhibit proteases such as aspartic acid proteases, for example HIV protease. Claim 7 is directed towards a method to administer a two or more isostere harboring protease inhibitor to a person infected with a pathogen expressing a protease. Claims 8 and 12 are directed to a method wherein the isosteres of the administered inhibitor are further defined and may comprise isosteres such as $-CH(OH)-CH_2-$, or substitutions thereof. Claims 10 and 11 are directed to defining the inhibitor to be administered in a method such that the inhibitor can be UIC-98-056 and may inhibit aspartic proteases such as HIV protease. Reasons for this grouping and arguments for the separate patentability of these groups of claims are provided below.

(8) ARGUMENTS

(a) The Claimed Invention

Aspartyl proteases have been widely studied and shown to be involved in the regulation of many proteins. These studies have incorporated genetic and biochemical, as well as structural observations. The implications drawn from these studies are that aspartyl acid proteases possess very similar active core structures and therefore exhibit a common mechanism of catalysis. Drug inhibitors that possess a "module" (isostere) that mimics the scissile bond normally cleaved by the core structure of the aspartyl protease were designed based on the correlation between

structure and mechanism. The inhibitor's ability to mimic the scissile bond and align it's peptide backbone with "subsites" in the core allows it to tightly bind in the core pocket. This mechanism is analogous to a "lock and key". Commercial inhibitors that harbor the isostere and thereby bind tightly, have been widely prescribed and used by patients to treat diseases such as AIDS by inhibiting aspartyl protease activity that is central to virus activity and replication. In fact, these inhibitors have been so widely used that there is an increased pressure on the aspartyl proteases, to which the inhibitor's interact and inhibit, to mutate so that they are no longer recognized by the single isostere harboring inhibitor(s). The appellants have discovered aspartyl protease inhibitors containing two or more isosteres have an increased efficacy in inhibiting the activity of such proteases by decreasing the protease's ability to become resistant to the inhibitory mechanism. The presence of two or more isosteres, while inhibiting the protease, also severely restricts or limits the ability of the protease to mutate to a form no longer recognizable by the compound.

The inhibitor (the "key") is structurally determined based upon the structure of the core (the "lock") of the aspartic protease that is required for normal protease activity. The appellants disclose in the specification that transition-state isosteres mimic a substrate peptide with a hydrolyzable site. The correct orientation of the isostere(s) within the core of the protease aids in determining binding and inhibitory efficacy. The proper orientation of the isostere(s) and the alignment of surrounding residues with subsites in the core, thereby providing tight binding, are precluded by the structure of the core of the protease. However, as stated above, based upon extensive analyses, the core of aspartyl proteases are structurally similar and exhibit common

mechanisms of catalysis. Therefore the structural features of the claimed inhibitors are clearly defined by the core structure of the well-studied asparyl protease family of enzymes. These findings provide the basis for the claimed aspartic protease inhibitor. The appellants have demonstrated how to design, make and test multi-isostere harboring aspartic protease inhibitors.

Appellants have discovered an increased efficacy of aspartyl protease activity inhibition and resistance by protease inhibitors harboring two or more isosteres. The appellants present in the specification the conceptual framework from which the Examples and data are derived. Conceptually, the invention revolves around the idea that enzymes, when consistently barraged with inhibitors, are posed with the difficult task of mutating, due to evolutionary pressure, in order to resist the inhibitor and ensure optimal activity. This task becomes even more difficult when more than just one mutation is required for resistance to the particular inhibitor. Example one and Figure III describe in detail and outline, respectively, the procedure for synthesizing a two isostere aspartyl protease inhibitor (HIV protease inhibitor UIC-98-056). The protease that encounters such an inhibitor will generally have to mutate at, at least, two residue positions to overcome the presence of two isosteres within it's core pocket. Multi-isostere harboring inhibitors align in the substrate binding site in two or more different ways, presenting different side chains for each alignment. Therefore, not only are the isosteres contributing to binding, they play a role in adjusting the interacting side chains of the inhibitor so that they also contribute to the overall binding. This mechanism makes it very unlikely that any one mutation in the protease can prevent binding of the inhibitor. The remarkable and surprising ability of UIC-98-056 (two-isostere inhibitor) to withstand the development of HIV protease mutation-resistance is

presented in Example two, Table II, and Figure four. The difference in the average increases in K_i for the resistant mutant HIV proteases, presented in Table II, over the wild type enzyme in the presence of inhibitor is truly unique and has not been previously reported. The average fold increase of resistance for the mutant proteases over wild type, in the presence of UIC-98-056, was only 1.45-fold (with 9 of the 10 K_i values unchanged from wild type), compared to 15.12-fold, 18.89-fold, and 10.76-fold for the commercially available drugs ritonavir, indinavir, and saquinavir, respectively. It should also be pointed out that if one were to disregard the fold increase for the I84V mutation, which is still less significant than the three commercially available drugs, there would actually be a decrease in average K_i for the nine remaining mutant proteases in the presence of UC-98-056 (0.56-fold).

The appellants also disclose pharmaceutical methods and formulations for the administration of the claimed inhibitors in light of those aspartyl protease inhibitors that are commercially available. For example, the treatment of HIV infected individuals using aspartyl protease inhibitors is well documented as disclosed in the specification (page 12, lines 26, to page 13, line 6). Similar types of methods and formulations may be used to administer the presently claimed inhibitors. The regimen and choice of drug and drug combinations are usually under the discretion of a physician and are dependent upon the resistance genotype and phenotype of the HIV strain.

(b) Rejections Under 35 U.S.C. § 112

Claims 1, 2, 4-8, and 10-12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification based on:

a) the prior art demonstrates the criticality of the choice and amount of compound and conditions effective to inhibit the protease; and

b) the claims encompass an unlimited number of types of compounds.

These rejections are factually, and legally, incorrect.

i. The Legal Standard under 35 U.S.C. § 112, first paragraph

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the

quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

ii. Factual Analysis of Claims 1, 2, 4-8, and 10-12 under 35 U.S.C. § 112, first paragraph (enablement).

The similarity of the core structure of the aspartyl proteases drives the common mechanistic features of enzymatic cleavage of proteins and polyprotein bonds within this class of proteins. The claimed aspartyl protease inhibitors are described in the specification. The process of making such an inhibitor that harbors two or more isosteres and assays used to measure it's inhibitory effects on various forms of HIV protease are provided within the examples. The claimed invention is based upon the detailed structural studies of the catalytic core of the HIV protease and other aspartyl proteases. These studies are outlined in the specification.

The *de novo* design of protease inhibiting compounds requires one to characterize the target protease as a member of a particular class, for example serine, cysteine, metallo, or aspartyl class (the aspartyl class being one the most extensively characterized). As stated on

page 3, line 29, to page 4, line 3 of the specification, the aspartic proteases share a common active-site structure (the "core") and catalytic mechanism. Designing an inhibitor relies upon this essential information because it is the activity of the core of the protease that is being inhibited. Once the core structure and/or catalytic mechanism has been elucidated, the design and construction of an inhibitor harboring two or more isosteres can be accomplished without undue experimentation, as provided for in the presently claimed invention. The design of inhibitors against aspartyl proteases, such as renin and HIV protease, has been demonstrated based upon this principal. Aspartyl protease inhibitors retain similar structural and physical properties because of their stereospecificity for a class of proteases with similar active pockets to which they bind and interact. Even if one was not familiar with the structural properties of a targeted enzyme, the amino acid sequence of the enzyme can be easily inserted into any number of commercially available computer programs and the structural features of the enzyme determined. The structure of the inhibitor is clearly limited based on the requirement for it to bind in the core of the targeted enzyme.

The appellants have provided, in the specification, examples and descriptions of isostere harboring aspartyl protease inhibitors, their standard modes of administration, as well as their formulation. 35 U.S.C. § 112, first paragraph, is satisfied in view of the combination of the art recognizing standard modes of making, formulating, and administering single isostere inhibitors; and the Example of making a two isostere inhibitor provided in the specification. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). The construction of the claimed inhibitors would not require

undue experimentation based upon: 1) the appellant's disclosed detailed method of making and testing the two isostere inhibitor; and 2) the structural characterization of the cores of aspartyl proteases, from which the presently claimed invention relies upon.

iii. Claims 1, 2, 4-8, and 10-12 were rejecter under 35 U.S.C. § 112, first paragraph (written description).

The Legal Standard

The leading case for the written description requirement in the biotechnology and pharmaceutical arts is *Eli Lilly v. Univ. of Calif. Board of Regents* In *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 (herein referred to as "the '525 patent") met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

In *Enzo Biochem*, the Federal Circuit held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). The Federal Circuit held that a patentee complied with the written description requirement by depositing biological material in a public depository. The specification described the nucleotide sequence in terms of its ability to bind to *N. gonorrhoeae*. The patent had issued with no written description rejection. Nevertheless, the

Federal Circuit had determined in *Enzo I* that, because the inventor had not described the actual nucleotide sequence of the probes in the patent specification, the written description was inadequate as a matter of law. In *Enzo II*, the Federal Circuit rejected its narrow interpretation of *Eli Lilly* that the disclosure of the sequence was always necessary, and instead adopted a broader interpretation of the types of disclosures that comply with the written description requirement. The court adopted provisions from the Guidelines issued by the U.S. Patent and Trademark Office that state that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. The court found that the written description requirement was met when, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure.

This standard has been reviewed and clarified further in the recent decision of Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003). This decision was the appeal of a lengthy district court ruling on validity, infringement, and enforceability of five Amgen patents relating to production of erythropoietin (EPO), a hormone that controls formation of red blood cells. Amgen's EPO is sold under the brand name EPOGEN®. Amgen asserted that Hoechst (now Aventis Pharmaceuticals, Inc.) and Transkaryotic Therapies ("TKT") infringed U.S. Patent No. 5,547,933; 5,618,698; 5,621,080; 5,756,349; and 5,955,422, due to the filing of TKT's Investigational New Drug Application (INDA). All of the patents shared the same disclosure. TKT recombinantly produced EPO using a method that differed from the method used by Amgen and described in the patents. TKT

inserted a promoter which caused the expression of ordinarily unexpressed endogenous (or "native") EPO DNA in human cells to produce the EPO.

The Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112. In rendering its decision, the Court continued in the manner of *Enzo II* and applied a broad interpretation of the types of disclosures that comply with the written description requirement. TKT asserted that claims did not meet the written description requirement since Amgen had failed to describe the use of all mammalian and vertebrate cells, relying on the earlier *Lilly* decision.

Relying heavily on the expert testimony provided in the District Court proceeding, the Federal Circuit held that this description adequately supports the claims covering EPO made using the genus vertebrate or mammalian cells.

One question that arose out of these proceedings was whether or not Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultures vertebrate cells that produce EPO. The district court in this case found that "the specification need teach only one mode of making and using a claimed composition." *Amgen, Inc v. Hoechst Marion Roussel, Inc* 126 F.Supp.2d 69, 160, 57 USPQ 2d 1449, 1515 (D.Mass.2001).

iv. Factual Analysis of Claims 1, 2, 4-8, and 10-12 under 35 U.S.C. § 112, first paragraph (written description).

The appellant had previously pointed out that the transition state isostere described at page 3, line 26 is merely a statement that characterizes a hydroxyethylene group mimicking the transition state of catalysis of an aspartic protease. This is an ***EXAMPLE*** of a transition state isostere. There are many other types of transition state isosteres directed to aspartic proteases, as taught at page 4, lines 5-8. However, "***in all cases....a single transition-state isostere is used in an inhibitor since it mimics a substrate peptide with a single hydrolysis site***" (emphasis added; see page 4, lines 5-8). As will be further described below, this form of mimicry (i.e. replacing the scissile bond of the substrate with a non-hydrolysable TS analog that mimics what is normally hydrolyzed by the protease), is ***the*** definition of a transition state analog.

It is well established that the one of the most common ways in which new molecules are designed involves the use of *known targets as starting points*. Well characterized targets allow for the proposed ligands to be evaluated in the binding site prior to synthesis. Indeed the most potent inhibitors of HIV-1 protease are peptidomimetics and are based on the transition-state (TS) mimic concept. This is very much state-of-the-art in pharmaceutical design involving a medicinal chemist designing inhibitors based on the optimal substrate. As described in the specification, the strategy involves replacing the scissile bond of the substrate with a non-hydrolysable TS analog that mimics this bond. The realization that HIV-1 protease belonged to the aspartic acid class of proteases has led many researchers to screen inhibitors of other aspartyl proteases (e.g. renin and pepsin). Such TS isosteres (already known from previous pepsin/renin work) mimic the tetrahedral intermediate formed in hydrolysis of the peptide.

In essence once a suitable TS mimic is found, amino acid residues in the optimal substrate are deleted/substituted with other moieties to find the optimal inhibitor. This uses both molecular modeling and structure determination (X-ray/NMR). *Much of the literature that claims to use* ***structure-based drug design*** *methods, model a candidate drug by placing it into the active site using a previously determined structure with the same TS mimic.* The TS mimic part of the drug is used to position the ligand. The other groups are then built in manually (using computer graphics). An evaluation of the quality of the candidate usually includes steric fit, hydrophobic and hydrogen bond interactions, and/or a highly favorable molecular mechanics energy (inter and intramolecular ligand energy), all of which can be determined by one of ordinary skill in the art. Suitable likely candidates are thus identified. These compounds are then tested for (1) binding affinity and if this proves promising, for (2) bioavailability and, again if this proves promising, (3) a structure would be determined. Successive rounds of such optimization allows one of ordinary skill to combine the characteristics of high affinity (as measured by IC50) and bioavailability (in animal tests). It should be noted that transition-state mimics and robust methods of lead modification have been, and continue to be, the mainstay of modern structure-based drug design.

(c) Rejections Under 35 U.S.C. § 102

i. The Legal Standard.

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987);

Scripps Clinic & Research Found v Genentech Inc, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling."

Paperless Accounting Inc v Bay Area Rapid Transit Sys., 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

ii. Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent Nos. 5,491,149 and 5,683,999 to Jadhav *et al.* ("Jadhav 1" and "Jadhav 2", respectively).

Jadhav 1

Jadhav 1 teaches substituted dihydroxypropylamines, and derivates thereof. The compounds taught by Jadhav decrease HIV viral yield and decrease multiplicity of the virus in human T cells *in vitro*. Jadhav 1 fails to contemplate two or more transition state isosteres in a polypeptide backbone, which have different orientations (see, for example, page 4, lines 31-32) the mimic the transition state of the aspartic acid protease. It should be noted that these different orientations are critical to stability, binding affinity, and efficacy with regard to protease inhibition and protease resistance mechanisms (see, for example, page 10, lines 10-20).

Jadhav 2

Jadhav 2 is directed to substituted cyclic urea compounds and derivatives thereof. The compounds of Jadhav 2 are taught as inhibiting HIV protease and thereby inhibiting HIV replication. Jadhav 2 fails to contemplate two or more transition state isosteres in a polypeptide backbone, which have different orientations (see, for example, page 4, lines 31-32) that mimic the transition state of the aspartic acid protease. The appellant respectfully submits that these different orientations are critical to stability, binding affinity, and efficacy with regard to protease inhibition and protease resistance mechanisms (see, for example, page 10, lines 10-20).

(d) The Examiner has failed to individually examiner the dependent claims.

It is well established that each claim must be separately examined for patentability. It is not enough, as here, to look at a single independent claim and reject all of the claims. No art or rationale has been presented as to why the subject matter of claims 2 and 8, wherein the specific formula for the claimed isostere is defined, is not definite and enabled.

The same argument is applicable to claims 6 and 12, wherein the specific formula of the isostere of claims 2 and 8, respectively, is substituted with two other isosteres.

The HIV protease aspartic acid site is well characterized. Several inhibitors consisting of a single isostere that binds tightly to this site are used clinically. No art or rational has been presented as to why the subject matter of claims 3 and 10 is not definite and enabled.

With regard to claims 5 and 11, drawn to a specific compound, the examiner indicates that this compound might be enabled, yet it is included under the rejection under 35 U.S.C. § 112, first paragraph, as overly broad and non-enabled.

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112,

first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

In this case, the examiner is relying on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure **and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement**. Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.
>
> *Id.* at 224.

The MPEP instructs examiners to make specific findings of *facts* to rebut Appellants' presumption and "specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation." MPEP at § 2164.05. The examiner should provide references to support a *prima facie* case of lack of enablement. *Id.*

The examiner has failed to meet the legal burden in this case.

(9) SUMMARY AND CONCLUSION

The appellant respectfully submits that when anticipation is based on inherency of limitations not expressly disclosed in the asserted anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991). In this case, neither of Jadhav 1 or Jadhav 2 contemplate protease inhibition *and combating protease resistance mechanisms as a result of utilizing different orientations of isosteres in an inhibitory compound.* Inherency cannot be based on the knowledge of the

inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *Cf. In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). The applicant further asserts that only in hindsight of the present application could one realize the nexus between protease inhibition and combating protease resistance mechanisms, and the utilization of two or more isosteres, each oriented differently.

Furthermore, as stated in the specification, many types of isosteres are well known and their mechanism of action is predictable based upon, for example, the fact that "a single transition-state isostere is used in an inhibitor since it mimics a substrate peptide with a single hydrolysis site". The isostere harboring drugs that have proven to be clinically effective and described for aspartyl protease inhibition, provide further evidence that isostere dependent inhibition is well known in the art. Therefore one of skill in the art would be very familiar with isostere structures and the processes to synthesize them.

The Examples explicitly outline a detailed procedure for making a multi-isostere harboring inhibitor (UIC-98-056). The construction of inhibitors harboring more than two isosteres would not require undue experimentation based upon the appellant's disclosed detailed method of making and testing the two isostere inhibitor (UIC-98-056), and the recognized art from which the presently claimed invention relies upon. The recognized art details the core structure of aspartyl proteases and mechanism of action. This art directly enables the scientific community to classify these proteases into one group. Based upon the common core structure of this particular class of proteases, to which the two or more isostere containing inhibitors bind and inhibit activity, the inhibitors are structurally defined in terms of size, physical and chemical

properties. In view of the foregoing discussion, Appellant's submit that the presently claimed invention is enabled for an aspartic protease harboring two or more isosteres, and a method for treating a patient infected with a pathogen expressing an aspartic acid protease administering the claimed protease inhibitor.

For the foregoing reasons, Appellant submits that the claims 1, 2, 4-8, and 10-12 are patentable.

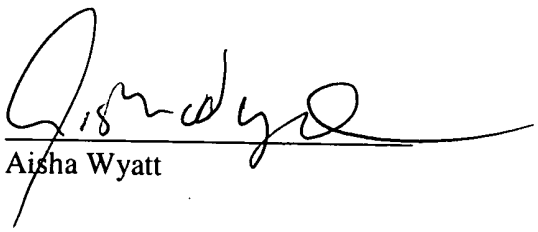
Respectfully submitted,

Todd S. Hofmeister
Reg. No. 53,029

Date: April 28, 2003
HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (fax)

Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.



Aisha Wyatt

Date: April 28, 2003

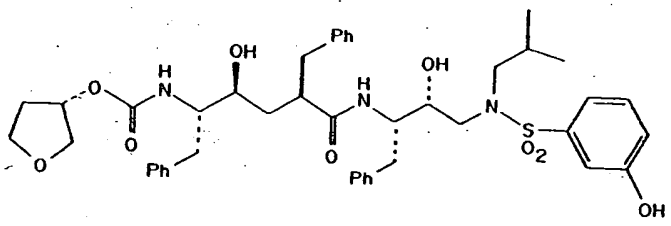
Appendix: Claims On Appeal

1. (twice amended) A polypeptide aspartic acid protease inhibitor comprising two or more transition-state isosteres in the polypeptide backbone, which have different orientations that mimic the transition state of the aspartic acid protease, and bind to different subsite binding pockets in the aspartic acid protease.

2. The inhibitor of claim 1 wherein the transition-state isostere is -CH(OH)-CH_2-.

4. (Amended) The composition of claim 1 wherein the aspartic acid protease inhibitor is an HIV protease inhibitor.

5. The inhibitor of claim 1 which is UIC-98-056 having the following structure:



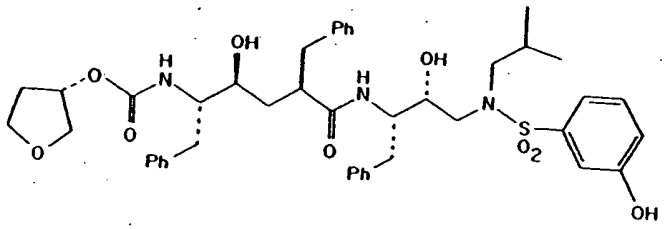
6. The inhibitor of claim 2 wherein the CH(OH)-CH_2 is substituted with two other kinds of isosteres.

7. (Amended) A method for treating a patient infected with a pathogen expressing an aspartic acid protease comprising the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

8. The method of claim 7 wherein the transition-state isostere is CH(OH)-CH_2-.

10. (Amended) The method of claim 7 wherein the protease inhibitor inhibits HIV protease.

11. The method of claim 10 wherein the inhibitor is UIC-98-056 having the following structure:



12. The method of claim 8 wherein the $CH(OH)-CH_2$ is substituted with two other kinds of isosteres.

TABLE OF CONTENTS

ii. Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent Nos. 5,491,149 and 5,683,999 to Jadhav *et al.* ("Jadhav 1" and "Jadhav 2", respectively).

(d) The Examiner has failed to individually examiner the dependent claims.

(9) SUMMARY AND CONCLUSION

Certificate of Mailing

Appendix: Claims On Appeal

Table of Contents

ATL1 #570227 v1